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**Saturated fat intake and prostate cancer aggressiveness: results from the population-based North Carolina-Louisiana Prostate Cancer Project**

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**Running title:** Saturated fat and aggressive prostate cancer

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## Abstract

**Background:** Epidemiologic and laboratory evidence supports a role for cholesterol in prostate cancer (PC). Dietary saturated fat content impacts serum cholesterol levels. However, epidemiologic associations between saturated fat and PC aggressiveness are inconsistent. We hypothesized that high saturated fat intake would be associated with increased PC aggressiveness, and that statin use would modify this association.

**Methods:** Of 1,854 PC cases in the North Carolina-Louisiana PC Project (PCaP), 321 (17%) were classified as high aggressive [Gleason sum  $\geq 8$ , PSA  $>20$  ng/ml, or (Gleason sum  $\geq 7$  and clinical stage T3-4)] or low/intermediate aggressive (all other cases). Using low/intermediate aggressive cases as the referent group, we examined the association between tertiles of total-fat adjusted saturated fat intake and high aggressive PC using logistic regression, overall and stratified by race and statin use. We examined total fat-adjusted polyunsaturated and monounsaturated fatty acids (PUFA and MUFA, respectively), trans fat, and cholesterol in secondary analysis.

**Results:** High total fat-adjusted saturated fat intake was associated with an elevated odds ratio (OR) for aggressive PC (OR<sub>T3vs.T1</sub> 1.51; 95% CI 1.10-2.06; p-trend=0.009), with an attenuated association in statin users (OR<sub>T3vs.T1</sub> 1.16; 95% CI 0.67-2.01; p-trend=0.661) compared to non-users (OR<sub>T3vs.T1</sub> 1.71; 95% CI 1.16-2.51; p-trend=0.053). High total fat-adjusted cholesterol intake was associated with aggressive PC in European Americans (OR<sub>T3vs.T1</sub> 1.62; 95% CI 1.02-2.58; p-trend=0.056), but not African Americans (OR<sub>T3vs.T1</sub> 0.92; 95% CI 0.60-1.42; p-trend=0.750). High total fat-adjusted PUFA was inversely associated with PC aggressiveness (OR<sub>T3vs.T1</sub> 0.75; 95% CI 0.55-1.03), although this was not significant. No associations were found between total fat-adjusted MUFA or trans fat and PC aggressiveness.

**Conclusions:** High total fat-adjusted saturated fat intake was associated with increased PC aggressiveness, with a suggestion of a stronger effect in men not using statins. The association between total fat-adjusted cholesterol intake and PC aggressiveness was most pronounced in European Americans.

## Introduction

Prostate cancer (PC) incidence rates vary more than 25-fold worldwide, and are highest in Western countries<sup>1</sup>. International variation in incidence rates is due in part to differences in screening practices between countries, but dietary factors may also play a role. Dietary fat intake, unlike other macronutrients, varies more than fivefold worldwide, and Western populations are among the highest consumers of saturated and trans fats, and cholesterol<sup>2</sup>.

High fat dietary interventions in mouse models of PC drive tumor growth<sup>3,4</sup>, but several large prospective cohort studies found no association between different types of dietary fat and PC risk<sup>5-7</sup>. However, some evidence supports an association between elevated intake of saturated fat and increased PC aggressiveness<sup>8,9</sup> and mortality<sup>8,10,11</sup>. Many prior studies were limited by incomplete assessment of potential confounders, including PC screening<sup>7</sup>. In addition, prior studies were primarily carried out in white populations, and so the impact of race on these associations remains poorly understood.

Using the North Carolina-Louisiana PC Project (PCaP), a case-only study of incident PC in European Americans (EAs) and African Americans (AAs), we examined associations between dietary saturated fat intake and PC aggressiveness, overall and stratified by race. Dietary saturated fat intake impacts serum cholesterol levels<sup>12</sup>, and epidemiologic evidence supports a role for serum cholesterol and cholesterol-lowering statins in PC<sup>13,14</sup>. Indeed, we previously reported an inverse association between statin use and PC aggressiveness in PCaP<sup>15</sup>. As such, we explored the hypothesis that the association between saturated fat and PC aggressiveness would be weaker in men using statins to control serum cholesterol levels. In secondary analysis, we examined associations between total fat, polyunsaturated fatty acid (PUFA), monounsaturated

fatty acid (MUFA), trans fat, cholesterol intake and PC aggressiveness.

## **Materials and Methods**

### *Study population*

PCaP enrolled men 40-79 years of age diagnosed with PC on or after July 1, 2004, as previously described<sup>16</sup>. Research subjects self-identified as either AA/black or Caucasian/white (EA) in response to the open-ended question “What is your race?” Recruitment ended October 2007 in North Carolina (NC) and July 2009 in Louisiana (LA). Research protocols were approved by the institutional review boards at the University of North Carolina, Louisiana State University Health Services Center, and Department of Defense PC Research Program.

### *Exposure assessment and explanatory variables*

PCaP research nurses administered questionnaires during an in-home visit approximately three months after diagnosis<sup>16</sup>. PC screening frequency was classified as a three-level variable (never screened,  $\leq 1$  PSA and/or digital rectal exam (DRE) per year,  $>1$  PSA and/or DRE per year), as previously described<sup>15</sup>. The dietary assessment instrument was a modified National Cancer Institute (NCI) Diet History Questionnaire (DHQ)<sup>17,18</sup> to which Southern US foods were added. Research subjects reported dietary intake during the 12 month period prior to PC diagnosis. Dietary intake of fatty acids and cholesterol was calculated using Diet\*Calc analysis software (version 1.4.3, NCI, Applied Research Program, November 2005). No gold standard exists for validating calories from dietary fats and cholesterol. However, a comparative validation study indicated that energy-adjusted correlations between multiple 24 hour recalls and DHQ estimates were 0.68 for saturated fat, 0.61 for PUFA, 0.60 for MUFA, 0.66 for total fat, and 0.64 for cholesterol<sup>17</sup>. Research subjects gathered all prescription medications used in the 2-week period prior to interview and presented them to the research nurse at the time of interview for



documentation of current statin use. We previously reported an inverse association between statin use and PC aggressiveness, with no differences in this association by statin type or dose<sup>15</sup>. Therefore, we did not consider statin type or dose in the present analysis.

### *Outcome assessment*

Clinical stage, biopsy Gleason sum, and serum PSA at diagnosis were abstracted from medical records. High aggressive PC, our outcome of interest, was defined as Gleason sum  $\geq 8$ , or PSA  $>20$  ng/ml, or (Gleason sum  $\geq 7$  and clinical stage T3-T4). Low/intermediate aggressive PC (all other cases) was used as the referent group for all analyses<sup>16</sup>. We excluded 85 research subjects lacking sufficient clinical data to define a PC aggressiveness category. We also excluded research subjects missing body mass index (BMI; n=21), PC screening frequency (n=221), smoking status (n=1), and those who reported implausibly low or high caloric intake ( $<800$  or  $\geq 6,000$  kcal/day, respectively; n=76). These exclusions resulted in 1,854 research subjects (n=993 EA and n=861 AA) for the present analysis.

### *Statistical analysis*

We examined differences in patient and tumor characteristics between low/intermediate versus high aggressive PC cases, and across tertiles of total fat-adjusted saturated fat intake, using chi-square tests for categorical variables, student's t-tests for continuous, normally-distributed variables and rank sum tests for continuous non-normally distributed variables.

Dietary variables were log transformed to improve normality. Saturated fat intake was adjusted for total fat intake using the residual method to examine the impact of saturated fat on PC aggressiveness independent of total fat intake<sup>19</sup>. Total fat-adjusted saturated fat intake was analyzed as a categorical variable, based on tertiles of the distribution among low/intermediate

aggressive PC cases. Logistic regression was used to estimate multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for associations between tertiles of total fat-adjusted saturated fat intake and PC aggressiveness (high vs. low/intermediate) using the lowest tertile (T1) as the referent. In secondary analysis, we explored race-specific tertiles of total fat-adjusted saturated fat intake. For multivariable analysis, we selected covariates using a directed acyclic graph and performed backwards selection to build our final model which included age (continuous), race (AA, EA), site (NC, LA), marital status (married/living as married, divorced/separated/widowed, single), BMI (continuous), statin use (yes, no), smoking status (never, former, current), PC screening frequency (never,  $\leq 1$  screening test per year,  $> 1$  screening test per year), energy intake (kcal; continuous), and energy-adjusted total fat intake (calculated using the residual method). Physical activity, education, income, Charleson comorbidity index, and family history of PC were dropped by backwards selection and therefore not included in the final model. Tests for trend of categorical variables were conducted by assigning each research subject the median value of their tertile of intake and modeling these values as a continuous variable. In secondary analysis, using the same method as described for total fat-adjusted saturated fat, we examined associations for tertiles of total fat-adjusted PUFA, MUFA, trans fat, and cholesterol intake and for tertiles of energy-adjusted total fat intake. We tested for interaction between race and dietary fat intake for predicting PC aggressiveness by incorporating a cross product term into the logistic regression model, and calculating the global p-value of the interaction term using the Wald test. We explored statin use as an effect modifier of associations between total fat-adjusted saturated fat intake and PC aggressiveness using models stratified by statin use.

Statistical analyses were performed using Stata 13.1 (Stata, Corp., College Station, TX, USA).

Statistical significance was two-sided with  $p < 0.05$ .

## Results

### *Demographic characteristics by PC aggressiveness*

Research subjects with high aggressive PC tended to be older at diagnosis, and were more likely to be AA than EA (Table 1). High aggressive PC cases were less likely to be married/living as married, less likely to report a history of PC screening, and had lower education and income levels than low/intermediate cases. Alcohol intake and level of physical activity did not differ by PC aggressiveness (data not shown), but research subjects with high aggressive disease were more likely to be current smokers and obese, and less likely to be statin users.

Saturated fat made up a larger percentage of total fat intake and PUFA made up a smaller percentage of total fat intake in research subjects with high versus low/intermediate aggressive PC, but there were no differences in percent MUFA or trans fat intake by PC aggressiveness (Table 1). Relative to research subjects with low/intermediate aggressive PC, those with high aggressive PC consumed a greater percentage of calories from total fat, and had higher cholesterol intake and higher daily energy intake. Dietary fat, cholesterol and energy intake by race are presented in Supplementary Table 1.

### *Demographic and tumor characteristics by tertiles of total fat-adjusted saturated fat intake*

Age at diagnosis did not differ by saturated fat intake, but AAs consumed less saturated fat than EAs (Table 2). Research subjects who consumed greater amounts of saturated fat were more likely to have high aggressive PC, less likely to be married/living as married and less likely to report a history of PC screening. Level of education, income, smoking, and obesity status did not differ across tertiles of total fat-adjusted saturated fat intake.

#### *Total fat-adjusted saturated fat, PUFA, MUFA and trans fat intake and PC aggressiveness*

Among 1,854 PC cases, 321 (n=175 AA and n=146 EA) had high aggressive disease. Relative to the lowest tertile, research subjects in the upper tertile of total fat-adjusted saturated fat intake had an elevated OR for high aggressive PC following adjustment for potential confounders (OR<sub>T3 vs. T1</sub> 1.51; 95% CI 1.10-2.06; *p-trend*=0.009; Table 3). Race-stratified analyses suggested that this effect was more pronounced in EAs (OR<sub>T3 vs. T1</sub> 1.96; 95% CI 1.23-3.12; *p-trend*=0.003) than AAs (OR<sub>T3 vs. T1</sub> 1.25; 95% CI 0.81-1.93; *p-trend*=0.321), but there was no significant interaction by race (*p-interaction*=0.452). We observed an inverse association between high total fat-adjusted PUFA intake and PC aggressiveness among all research subjects (OR<sub>T3 vs. T1</sub> 0.75; 95% CI 0.55-1.03; *p-trend*=0.075), with a similar magnitude of inverse association in both EAs and AAs although neither overall nor race-stratified findings were statistically significant (Table 3). There were no significant associations between total fat-adjusted MUFA or trans fat intake and PC aggressiveness, overall or in race-stratified analyses. The magnitude and direction of association between tertiles of energy-adjusted total fat intake and PC aggressiveness was similar to that reported for total fat-adjusted saturated fat intake (Table 3). The use of race-specific tertiles of dietary fat intake did not substantially impact our findings (Supplementary Table 2).

#### *Total fat-adjusted cholesterol intake and PC aggressiveness*

High total fat-adjusted cholesterol intake was associated with increased PC aggressiveness in EAs (OR<sub>T3 vs. T1</sub> 1.62; 95% CI 1.02-2.58; *p-trend*=0.056) but not AAs (OR<sub>T3 vs. T1</sub> 0.92; 95% CI 0.60-1.42; *p-trend*=0.750), although the interaction by race was not statistically significant (*p-interaction*=0.244). Analyses using race-specific tertiles of total fat-adjusted cholesterol intake produced similar findings (Supplementary Table 2).

*Statin use as an effect modifier of the saturated fat - PC aggressiveness association*

Analyses stratified by statin use showed that research subjects in the upper tertile of total fat-adjusted saturated fat intake had an elevated OR for high aggressive PC regardless of statin use status. However, there was a weaker association in statin users ( $OR_{T3 \text{ vs. } T1} 1.16$ ; 95% CI 0.67-2.01;  $p\text{-trend}=0.661$ ) compared to non-users ( $OR_{T3 \text{ vs. } T1} 1.71$ ; 95% CI 1.16-2.51;  $p\text{-trend}=0.053$ ; Table 4), although there was no significant interaction by statin use ( $p\text{-interaction}=0.430$ ).

## Discussion

Using data from the population-based, case-only PCaP, we report that elevated dietary intake of saturated fat was associated with increased PC aggressiveness. In secondary analysis, we found that higher total fat intake was also associated with more aggressive disease. Although there was no strong evidence for racial differences in these associations, effect estimates for total and saturated fat were larger in EAs relative to AAs, and high dietary cholesterol was associated with higher PC aggressiveness only in EAs. These findings support a role for dietary fat intake in PC aggressiveness in both EA and AA men, although future studies are required to test the suggestion that these associations may be stronger in EAs.

Relatively few studies to date have examined associations between dietary fat and PC by race. The prospective Multiethnic Cohort (MEC) study reported no associations between any type of dietary fat or cholesterol intake and either total or aggressive PC risk in any of five racial/ethnic groups examined<sup>5</sup>. A case-control study of four different racial/ethnic groups in North America reported a positive association between saturated fat intake and PC risk in both EAs and AAs<sup>20</sup>. Two studies indirectly assessed saturated fat intake by measuring red meat and animal fat consumption; one multi-center case-control study in the US showed a positive association between animal fat intake and aggressive disease in both EAs and AAs<sup>21</sup>, while the prospective Cancer Prevention Study II reported stronger associations between red meat consumption and PC risk in AAs<sup>22</sup>. Collectively, the findings of these prior studies and those of the present analysis do not provide strong evidence for racial differences in associations between dietary fat and cholesterol intake and PC aggressiveness and if a racial difference exists, the difference appears small.

A number of biologic mechanisms may contribute to associations between dietary fat and PC aggressiveness. High fat diets can modulate androgen signaling<sup>23</sup>, up-regulate the insulin-like growth factor (IGF) pathway, and increase prostate inflammation, thereby promoting PC growth<sup>24,25</sup>. Moreover, saturated fat intake is an important dietary determinant of serum cholesterol levels<sup>12,26</sup>. Epidemiologic data support a positive association between high serum cholesterol and PC aggressiveness<sup>27</sup> and an inverse association between statin use and PC aggressiveness<sup>15,28</sup>. If saturated fat intake promotes PC aggressiveness by raising serum cholesterol levels, the association between saturated fat and PC aggressiveness should be attenuated in individuals using statins to control serum cholesterol levels. We observed a weaker magnitude of effect in statin users, but found no strong evidence to support statin use as an effect modifier of the saturated fat-PC aggressiveness association. These findings may reflect the complex relationship between saturated fat and PC aggressiveness, given multiple determinants (both dietary and genetic) of serum cholesterol levels, in addition to the aforementioned cholesterol-independent mechanisms by which saturated fat may impact PC aggressiveness.

Epidemiologic evidence supporting an association between PUFA intake and PC aggressiveness is sparse and inconsistent. Individual studies have reported positive<sup>6</sup>, inverse<sup>29</sup> and null associations<sup>8</sup>, and a recent meta-analysis reported a null association between PUFA intake and risk of both total and aggressive PC<sup>7</sup>. Furthermore, a recent systematic review found no consistent role for fish oil, an important source of omega-3 PUFAs, in reducing PC incidence, aggressiveness, or mortality<sup>30</sup>. In the present study, although the direction of association between PUFA intake and PC aggressiveness was inverse, these findings were not statistically significant either overall or in race-stratified analysis.



Several limitations of this study should be considered. First, although we used a validated FFQ in the present study, FFQs are subject to recall bias and may be influenced by case status of the research subject. However, given that all of our research subjects were incident PC cases, this potential source of bias is likely to be minimal. Furthermore, the use of rapid case ascertainment limited the time between diagnosis and enrollment in PCaP, thus reducing the likelihood of bias from time or treatment. Second, serum levels of fatty acids and cholesterol were not measured in PCaP as measurements at the time of diagnosis may be impacted by presence of PC, raising concerns about reverse causality<sup>31</sup>. Measurement of dietary fat intake using a validated FFQ may be less subject to this potential source of bias. These limitations are balanced by several important strengths. All types of dietary fat and cholesterol were adjusted for total fat intake using the residual method, and models were adjusted for energy-adjusted total fat intake and energy intake. This approach separated the effects of each fat type from total fat on PC aggressiveness while controlling for energy intake. Finally, an important strength of this study is the inclusion of both EAs and AAs in similar proportions, in addition to our comprehensive assessment of clinical and demographic characteristics and adjustment for these potential confounders in our analysis.

In summary, elevated dietary intake of saturated and total fat were associated with increased PC aggressiveness. Although we observed no statistically significant racial differences in these associations, high saturated and total fat intake were suggestively more strongly associated with PC aggressiveness in EAs, and cholesterol was associated with higher PC aggressiveness in EAs but not in AAs. Established PC risk factors, including older age, AA race, and family history of PC, are not modifiable. If confirmed, these findings may be relevant for aggressive PC prevention efforts, given that dietary fat content and composition are modifiable risk factors.

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**Table 1:** Characteristics of research subjects with low/intermediate versus high aggressive prostate cancer

	Prostate cancer aggressiveness		<i>p-value</i>
	Low/intermediate	High	
<b>Age at diagnosis, mean (SD)</b>	62.6 (7.9)	64.7 (7.6)	<0.0001
<b>Race, n (%)</b>			
European American	847 (55)	146 (45)	0.001
African American	686 (45)	175 (55)	
<b>Site, n (%)</b>			
North Carolina	751 (49)	138 (43)	0.050
Louisiana	782 (51)	183 (57)	
<b>Marital status, n (%)</b>			
Single/never married	58 (4)	21 (7)	<0.0001
Divorced/separated/widowed	260 (17)	82 (26)	
Married/living as married	1,215 (79)	218 (68)	
<b>Screening frequency, n (%)</b>			
Never	234 (15)	98 (31)	<0.0001
≤1 PSA/DRE test per year	947 (62)	167 (52)	
>1 PSA/DRE test per year	352 (23)	56 (17)	
<b>Education, n (%)</b>			
Less than high school	249 (16)	88 (27)	<0.0001
High school graduate	378 (25)	69 (22)	
College graduate or some college	905 (59)	164 (51)	
<b>Income<sup>‡</sup>, (%)</b>			
<\$20,000	246 (17)	89 (31)	<0.0001
\$20,000-\$50,000	476 (34)	95 (33)	
\$50,000-\$80,000	309 (22)	47 (16)	
>\$80,000	378 (27)	57 (20)	
<b>Smoking status, n (%)</b>			
Never	537 (35)	89 (28)	<0.0001
Past	796 (52)	165 (51)	
Current	200 (13)	67 (21)	
<b>BMI (kg/m<sup>2</sup>), n (%)</b>			
<25	287 (19)	55 (17)	0.041
25-30	678 (44)	123 (38)	
≥30	568 (37)	143 (45)	
<b>Statin use, n (%)</b>			
No	932 (61)	214 (67)	0.049
Yes	601 (39)	107 (33)	
<b>Saturated fat (% total fat), mean (SD)</b>	31.0 (4.5)	31.9 (4.7)	0.001
<b>PUFA (% total fat), mean (SD)</b>	23.3 (4.2)	22.5 (4.4)	0.005
<b>MUFA (% total fat), mean (SD)</b>	38.2 (2.6)	38.1 (2.4)	0.747
<b>Trans fat (% total fat), mean (SD)</b>	6.2 (1.7)	6.3 (1.7)	0.409
<b>Total fat (% energy), mean (SD)</b>	34.0 (6.8)	34.9 (7.1)	0.040
<b>Cholesterol (mg/day), median (IQR)</b>	272 (186-371)	304 (222-421)	0.0001
<b>Energy intake (kcal/day), median (IQR)</b>	2,253 (1,713-3,000)	2,450 (1,802-3,324)	0.006

<sup>‡</sup>n=41 did not know their income and n=116 refused to answer this question; n=1 was missing education

**Table 2:** Characteristics of research subjects by tertile of total fat-adjusted saturated fat intake

	Total fat-adjusted saturated fat <sup>‡</sup>			p value
	T1	T2	T3	
<b>Age at diagnosis, mean (SD)</b>	63.5 (7.6)	62.0 (7.9)	63.4 (8.2)	0.189
<b>Race, n (%)</b>				<0.0001
European American	288 (48)	306 (50)	399 (62)	
African American	309 (52)	304 (50)	248 (38)	
<b>Site, n (%)</b>				0.317
North Carolina	275 (46)	307 (50)	307 (47)	
Louisiana	322 (54)	303 (50)	340 (53)	
<b>Aggressive prostate cancer, n (%)</b>				0.006
Low/Intermediate	511 (86)	511 (84)	511 (79)	
High	86 (14)	99 (16)	136 (21)	
<b>Marital status, n (%)</b>				<0.0001
Single/never married	19 (3)	31 (5)	29 (5)	
Divorced/separated/widowed	86 (14)	104 (17)	152 (23)	
Married/living as married	492 (82)	475 (78)	466 (72)	
<b>Screening frequency, n (%)</b>				0.029
Never	83 (14)	115 (19)	134 (21)	
<1 PSA/DRE test per year	381 (64)	358 (59)	375 (58)	
>1 PSA/DRE test per year	133 (22)	137 (22)	138 (21)	
<b>Education, n (%)</b>				0.355
Less than high school	102 (17)	102 (17)	133 (21)	
High school graduate	140 (24)	150 (25)	157 (24)	
College graduate or some college	355 (59)	357 (58)	357 (55)	
<b>Income<sup>†</sup>, n (%)</b>				0.340
<\$20,000	98 (18)	103 (18)	134 (23)	
\$20,000-\$50,000	186 (34)	190 (34)	195 (33)	
\$50,000-\$80,000	115 (21)	123 (22)	118 (20)	
>\$80,000	150 (27)	148 (26)	137 (24)	
<b>Smoking status, n (%)</b>				0.093
Never	214 (36)	203 (33)	209 (32)	
Past	316 (53)	314 (52)	331 (51)	
Current	67 (11)	93 (15)	107 (17)	
<b>BMI (kg/m<sup>2</sup>), n (%)</b>				0.586
<25	109 (18)	111 (18)	122 (19)	
25-30	273 (46)	254 (42)	274 (42)	
≥30	215 (36)	245 (40)	251 (39)	
<b>Statin use, n (%)</b>				0.046
No	384 (64)	353 (58)	409 (63)	
Yes	213 (36)	257 (42)	238 (37)	

<sup>†</sup>n=41 did not know their income and n=116 refused to answer this question; n=1 was missing education

<sup>‡</sup>saturated fat was adjusted for total fat intake using the residual method



**Table 3:** Odds ratios for aggressive prostate cancer according to tertiles of total fat-adjusted dietary fat and cholesterol intake, overall and stratified by race

	All		European American		African American	
	n, low/intermediate (high aggressive)	OR* (95% CI)	n, low/intermediate (high aggressive)	OR* (95% CI)	n, low/intermediate (high aggressive)	OR* (95% CI)
<b>Saturated fat<sup>‡</sup></b>						
T1	511 (86)	1.00 (ref)	256 (32)	1.00 (ref)	255 (54)	1.00 (ref)
T2	511 (99)	1.17 (0.84-1.62)	268 (38)	1.23 (0.73-2.07)	243 (61)	1.05 (0.68-1.63)
T3	511 (136)	1.51 (1.10-2.06)	323 (76)	1.96 (1.23-3.12)	188 (60)	1.25 (0.81-1.93)
<i>p-trend</i>		0.009		0.003		0.321
<b>PUFA<sup>‡</sup></b>						
T1	511 (126)	1.00 (ref)	314 (61)	1.00 (ref)	197 (65)	1.00 (ref)
T2	511 (106)	0.89 (0.66-1.20)	262 (47)	0.99 (0.64-1.53)	249 (59)	0.78 (0.51-1.19)
T3	511 (89)	0.75 (0.55-1.03)	271 (38)	0.70 (0.44-1.11)	240 (51)	0.73 (0.48-1.13)
<i>p-trend</i>		0.075		0.154		0.157
<b>MUFA<sup>‡</sup></b>						
T1	511 (107)	1.00 (ref)	297 (53)	1.00 (ref)	214 (54)	1.00 (ref)
T2	511 (118)	1.03 (0.77-1.40)	282 (56)	1.07 (0.70-1.65)	229 (62)	0.95 (0.61-1.46)
T3	511 (96)	0.89 (0.65-1.22)	268 (37)	0.81 (0.50-1.30)	243 (59)	0.99 (0.64-1.53)
<i>p-trend</i>		0.509		0.436		0.956
<b>Trans fat<sup>‡</sup></b>						
T1	511 (101)	1.00 (ref)	332 (58)	1.00 (ref)	179 (43)	1.00 (ref)
T2	511 (109)	0.98 (0.72-1.33)	270 (55)	1.20 (0.79-1.83)	241 (54)	0.82 (0.51-1.30)
T3	511 (111)	0.97 (0.71-1.33)	245 (33)	0.76 (0.47-1.23)	266 (78)	1.09 (0.70-1.70)
<i>p-trend</i>		0.857		0.376		0.584
<b>Total fat<sup>‡</sup></b>						
T1	511 (96)	1.00 (ref)	230 (28)	1.00 (ref)	281 (68)	1.00 (ref)
T2	511 (99)	1.12 (0.82-1.55)	287 (42)	1.18 (0.70-1.99)	224 (57)	1.14 (0.75-1.72)
T3	511 (126)	1.48 (1.08-2.02)	330 (76)	1.84 (1.13-2.98)	181 (50)	1.19 (0.77-1.83)
<i>p-trend</i>		0.016		0.010		0.408
<b>Cholesterol<sup>‡</sup></b>						
T1	511 (94)	1.00 (ref)	319 (49)	1.00 (ref)	192 (45)	1.00 (ref)
T2	511 (98)	0.92 (0.66-1.26)	311 (47)	1.02 (0.65-1.59)	200 (51)	0.85 (0.53-1.36)

T3 <i>p-trend</i>	511 (129)	1.16 (0.85-1.58) <i>0.369</i>	217 (50)	1.62 (1.02-2.58) <i>0.056</i>	294 (79)	0.92 (0.60-1.42) <i>0.750</i>
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\*adjusted for age, race (except for analyses stratified by race), site, marital status, BMI, statin use, smoking status, prostate cancer screening frequency, energy-adjusted total fat intake (except for total fat analyses) and energy intake

†adjusted for total fat intake using the residual method (with the exception of total fat which was adjusted for energy intake using the residual method)

**Table 4:** Associations between tertiles of total fat-adjusted saturated fat intake and prostate cancer aggressiveness stratified by statin use

	Statin non-users		Statin users	
	n, low/intermediate (high aggressive)	OR* (95%CI)	n, low/intermediate (high aggressive)	OR* (95%CI)
<b>Saturated fat<sup>‡</sup></b>				
T1	328 (56)	<i>1.00 (ref)</i>	183 (30)	<i>1.00 (ref)</i>
T2	292 (61)	1.21 (0.80-1.84)	219 (38)	1.03 (0.60-1.78)
T3	312 (97)	1.71 (1.16-2.51)	199 (39)	1.16 (0.67-2.01)
<i>p-trend</i>		<i>0.053</i>		<i>0.661</i>

\*adjusted for age, race, site, marital status, BMI, smoking status, prostate cancer screening frequency, energy-adjusted total fat intake, and energy intake

<sup>‡</sup>saturated fat was adjusted for total fat intake using the residual method